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Obesity and the kidney: Why is the kidney at risk?

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Two recent studies may help to account for the increase in risk of renal injury associated with obesity. One study pointed to a role for renin-system activation. In the other study, the pattern of renal hemodynamics was compatible with a renin mechanism.

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In this issue of *Kidney International*, Krikken *et al.*[1] describe an interesting set of relationships between body mass index (BMI), salt intake, glomerular filtration rate, and filtration fraction in healthy young men. Ten years ago, these relationships would probably have been of interest to only a small number of people, those fascinated by details of how the kidney works. Today, the interest will be substantially greater. Why? About ten years ago, Ribstein *et al.* described the effects of overweight and hypertension on the kidney.[2] Over the ensuing several years, there has been a rapid accumulation of information to suggest that obesity negatively influences the kidney, placing it at increased risk of injury and end-stage disease.[3–8] Why should that be?

Krikken *et al.*[1] point out in their Discussion, quite correctly, that this study was not designed to assess mechanisms. They cite a number of possible explanations, including a recently published work from our laboratory on the renin system and obesity in healthy individuals.[9] Both studies focus on healthy young people and measure renal hemodynamics as their end point, and they are almost certainly addressing the same issue. They differ in several ways. In our study,[9] the primary end point was the influence of captopril or an angiotensin receptor blocker on renal perfusion. As the response to captopril and to the angiotensin receptor blocker was essentially identical, we can assume that the measure provides an index of the contribution of the renin system to renovascular tone. The study was positive: increasing BMI was associated with an increase in renovascular response to interruption of the renin system.

The substudies also differ in the frequency of obesity: Both the study in Holland[1] and the study in the United States[9] recruited subjects without reference to their BMI. Only two of the 95 Dutch had a BMI over 30.[1] Twenty-two of 100 had a BMI over 30 in the United States.[9]

The relationship was not linear: indeed, for the first time in my scientific career, a quadratic function provided a best fit.[9] The vasodilator response to angiotensin-converting enzyme inhibition began to increase at a BMI of 25 but became substantially greater at a BMI exceeding 30 (Figure 1).

These two studies raise important questions. One involves the mechanism for renin-system activation. There are a number of candidates. The second, probably more important, is what we should do about it. As so many of our patients at risk of end-stage renal disease are obese, it is reasonable to wonder whether dealing with the obesity will improve the natural history. There is an anecdotal literature to indicate that bariatric surgery, when effective in reducing body mass, can reverse hypertension and reverse proteinuria in patients with diabetes and nephropathy. Probably, we ought to be discussing what that means for our patients.

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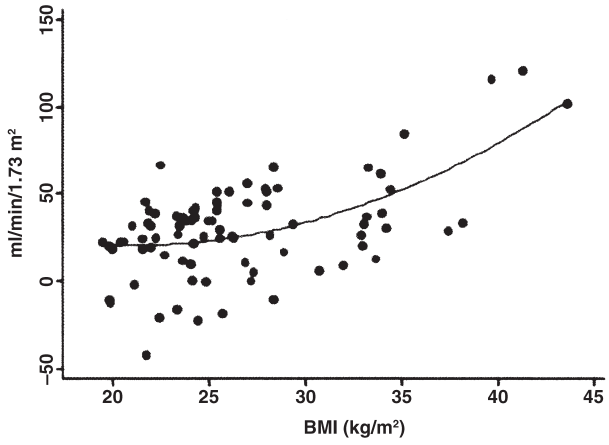

Figure 1| Relation between body mass index (BMI) and the renal plasma flow (RPF) response to captopril in healthy volunteers. Note that the data were best fit by a quadratic. The RPF response began to increase in those who were overweight (BMI 25–30 kg/m^2) and then rose much more quickly in those who were obese (BMI > 30 kg/m^2). (Reprinted from ref. 9.)

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Is it the low-protein diet or simply the salt restriction?

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Dietary factors, such as salt and protein intake, may play an important role in the progression of kidney disease. Consequently, dietary manipulations of these constituents are of interest both in experimental models of kidney disease and in clinical trials with patients with chronic kidney disease to assess whether modification of these exposures will result in a stabilization of disease progression.

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Chronic kidney disease (CKD) is a more common clinical problem that once thought and is frequently associated with substantial cardiovascular morbidity and mortality. It is well recognized that better control of blood pressure is important in mitigating the progression of CKD. In addition, pharmacological manipulation of the renin–angiotensin system plays an important role as part of an effective blood pressure-lowering strategy in reducing the rate of progression of kidney disease. It is also recognized that dietary factors may also be important in the rate of progression of kidney disease.[1] Both dietary protein and salt have been implicated as targets for manipulation to limit progression of kidney disease.

When the Modification of Diet in Renal Disease study was completed more than a decade ago, it was assumed that blood pressure, and not intensive dietary protein restriction, was the critical factor in limiting the progression of kidney disease.[2] However, it is important to note that in the Modification of Diet in Renal Disease study the majority of patients received angiotensin-converting enzyme inhibitors and calcium channel blockers, achieved the respective target blood pressure goals, and had intensive dietary education to achieve a daily salt intake of approximately 1 g. It is quite likely that improved blood pressure control, angiotensin-converting enzyme inhibition, and dietary salt restriction mitigated the potential benefits of a very-low-protein diet in delaying the progression of kidney disease. Moreover, the trial design did not use a washout period to remove from the analysis the initial hemodynamic decrease of glomerular filtration rate in response to the reduction of protein intake. It is also important to note that reduction in dietary protein can reduce glomerular filtration rate, hyperfiltration, and proteinuria, which could be helpful in mitigating the progression of kidney disease. I suspect that more effort has not been focused on dietary protein restriction because of concerns about impairing nutrition, which is particularly important in patients with more advanced kidney disease, and problems of cost and compliance with specialized lower-protein diets.

In an interesting paper, Bellizzi *et al.*[3] (this issue) report their evaluation of a very-low-protein diet supplemented with ketoanalogs in patients with stage 4 and stage 5 kidney disease. This study is reminiscent of the Modification of Diet in Renal Disease study and incorporated the same types of patients with more advanced forms of kidney disease. The authors clearly demonstrate that those patients on the very-low-protein diet achieved a statistically significant reduction of blood pressure despite concurrent reduction in antihypertensive medication. Moreover, they demonstrate that urine urea correlated with reduced urinary sodium excretion and that blood pressure reduction was independently related to urinary sodium excretion and the very-low-protein diet restriction, but not the level of protein intake. Their working hypothesis with these results raised the question of why the very-low-protein diet was effective in reducing the blood pressure. Was it simply reduced dietary sodium intake, or the type of vegetable proteins in the very-low-protein diet, or the ketoanalog supplementation, which could provide a vasodilator effect of branched-chain essential amino acids? Although the authors are fair in providing a balanced perspective in this regard, I find it quite likely that the majority of the effects are related simply to reduced dietary salt exposure. The authors importantly noted that there was a correlation between decreased fractional

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